REMARKS

Claims 2-3, 5-9, and 11-23 are pending in the subject application with claims 11-16 and 18-23 withdrawn from consideration. Applicants have not cancelled, added, or amended any claims herein.

Claims Rejected Under 35 U.S.C. § 103(a)

Claims 2-3, 6-8, and 17

The Examiner has maintained the rejection of claims 2-3, 6-8, and 17 under 35 U.S.C. § 103(a) as allegedly obvious over Ronai et al. (*Biochem. Biophys. Res. Comm.*, 1979, 91:1239-49) in view of Abbruscato et al. (*J. Neurochem.*, 1997, 69: 1236-45) and Kanai et al. (*J. Biol. Chem.*, 1998, 273: 23629-32). The Examiner asserted that it would have been obvious to one of skill in the art, in light of Kanai et al., to substitute methionine for the alanine in biphalin taught by Abbruscato et al. in order to mimic the tetrapeptide taught by Ronai et al.

The Examiner asserted that the March 28, 2009 Declaration Under 37 C.F.R. § 1.132 of Andrzej W. Lipkowski submitted with Applicants' April 2, 2009 response is insufficient to overcome the obviousness rejection. The Examiner stated that the Declaration indicates that the duration of anti-nociception of the two monomers, Tyr-D-Ala-Gly-Phe-NH_2 and Tyr-D-Met-Gly-Phe-NH_2, was found to be comparable for the same dosage tested, but fails to provide data to indicate what is meant by "comparable." The Examiner stated that the unexpected duration of anti-nociception shown by the claimed dimer over biphalin will remain unconvincing until data comparing the two monomers is provided.

In response, Applicants respectfully traverse the rejection. Applicants attach hereto as **Exhibit 1** a May 31, 2010, 2010 Declaration Under 37 C.F.R. § 1.132 of Andrzej W. Lipkowski. The Declaration presents results of experiments performed to determine the duration of anti-nociception elicited by the "biphalin monomer," Tyr-D-Ala-Gly-Phe-NH_2, and the monomer of the claimed invention, Tyr-D-Met-Gly-Phe-NH_2.

As disclosed in Exhibit 1, Tyr-D-Met-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe-NH_2 exhibit comparable durations of anti-nociception. Specifically, at a dose of 2 nmol, both monomers show levels of anti-nociception of 0% MPE at 120 minutes post-administration. However, biphalin and the claimed dimer do not exhibit comparable durations of anti-nociception, as indicated in paragraphs 4 and 5 of the March 28, 2009 Declaration. Specifically, at 120 minutes post-administration, the claimed dimer shows 30% anti-nociceptive activity while biphalin shows 0% MPE anti-nociceptive activity. The sustained anti-nociceptive activity of the claimed dimer over biphalin could not have been predicted by one of ordinary skill in the art in view of the evidence showing the comparable duration of anti-nociceptive activity of the two monomers.

Accordingly, Applicants maintain that the claimed dimer is not obvious over the combination of cited references and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 2-3, 5-9, and 17

The Examiner has maintained the rejection of claims 2-3, 6-8, and 17 under 35 U.S.C. § 103(a) as allegedly obvious over Ronai et

al. (*Biochem. Biophys. Res. Comm.*, 1979, 91:1239-49), Abbruscato et al. (*J. Neurochem.*, 1997, 69: 1236-45), and Kanai et al. (*J. Biol. Chem.*, 1998, 273: 23629-32) as applied to claims 2-3 and 6-8 in further view of Hill et al. (U.S. Patent No. 5,880,132), Bock et al. (EP 0434369 A1), and Ornstein (U.S. Patent No. 5,356,902).

The Examiner asserted that Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds. The Examiner asserted that Hill et al. teaches pharmaceutical compositions comprising both piperidine tachykinin antagonists and opioid analgesics. The Examiner asserted that Bock et al. teach cholecytokinin antagonists and their ability to potentiate morphine and other analgesics. The Examiner alleged that it would have been obvious to one of ordinary skill in the art to combine the claimed compound as allegedly taught by the combination of Ronai et al, Abbruscato et al. and Kanai et al., with the stimulatory amino acid, tackykinin, or cholecystokinin receptor antagonists taught by Ornstein, Hill et al., and Bock et al. or the biphalin taught by Abbruscato et al.

The Examiner asserted that the March 28, 2009 Declaration Under 37 C.F.R. § 1.132 of Andrzej W. Lipkowski submitted with Applicants' April 2, 2009 response is insufficient to overcome the obviousness rejection. The Examiner stated that the Declaration indicates that the duration of anti-nociception of the two monomers, Tyr-D-Ala-Gly-Phe-NH_2 and Tyr-D-Met-Gly-Phe-NH_2, was found to be comparable for the same dosage tested, but fails to provide data to indicate what is meant by "comparable." The Examiner stated that the unexpected duration of anti-

nociception shown by the claimed dimer over biphalin will remain unconvincing until data comparing the two monomers is provided.

In response, Applicants respectfully traverse the rejection. Applicants attach hereto as **Exhibit 1** a May 31, 2010 Declaration Under 37 C.F.R. § 1.132 of Andrzej W. Lipkowski. The Declaration presents results of experiments performed to determine the duration of anti-nociception elicited by the "biphalin monomer," Tyr-D-Ala-Gly-Phe-NH_2, and the monomer of the claimed invention, Tyr-D-Met-Gly-Phe-NH_2.

As disclosed in Exhibit 1, Tyr-D-Met-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe-NH_2 exhibit comparable durations of anti-nociception. Specifically, at a dose of 2 nmol, both monomers show levels of anti-nociception of 0% MPE at 120 minutes post-administration. However, biphalin and the claimed dimer do <u>not</u> exhibit comparable durations of anti-nociception, as indicated in paragraphs 4 and 5 of the March 28, 2009 Declaration. Specifically, at 120 minutes post-administration, the claimed dimer shows 30% anti-nociceptive activity while biphalin shows 0% MPE anti-nociceptive activity. The sustained anti-nociceptive activity of the claimed dimer over biphalin could not have been predicted by one of ordinary skill in the art in view of the evidence showing the comparable duration of anti-nociceptive activity of the two monomers.

Accordingly, Applicants maintain that the claimed dimer is not obvious over the combination of cited references and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney

invites the Examiner to telephone him at the telephone number provided below.

No fee, other than the enclosed total fee of $960.00, is deemed necessary in connection with the filing of this Communication and RCE. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

Gary J. Gershik
Registration No. 39,992
Attorney for Applicants
Cooper & Dunham, LLP
30 Rockefeller Plaza
New York, New York 10112
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Gary J. Gershik 6/11/10

Gary J. Gershik Date
Reg. No. 39,992

EXHIBIT 1